US006277975B1

(12) **United States Patent**
Larsen et al.

(10) **Patent No.: US 6,277,975 B1**
(45) **Date of Patent: *Aug. 21, 2001**

(54) **FUSIONS OF P-SELECTIN LIGAND PROTEIN AND POLYNUCLEOTIDES ENCODING SAME**

(75) Inventors: **Glenn R. Larsen**, Sudbury; **Dianne S. Sako**, Boston; **Xiao-Jia Chang**, Newton Centre; **Geertruida M. Veldman**, Sudbury; **Dale Cumming**, Acton; **Ravindra Kumar**, Belmont; **Gray Shaw**, Cambridge, all of MA (US)

(73) Assignee: **Genetics Institute, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/713,556**

(22) Filed: **Aug. 30, 1996**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/428,734, filed on Apr. 25, 1995, now Pat. No. 5,843,707, which is a continuation-in-part of application No. 08/316,305, filed on Sep. 30, 1994, now abandoned, which is a continuation-in-part of application No. 08/235,398, filed on Apr. 28, 1994, now abandoned, which is a continuation-in-part of application No. 08/112,608, filed on Aug. 26, 1993, now abandoned, which is a continuation-in-part of application No. 07/965,662, filed on Oct. 23, 1992, now abandoned.

(51) **Int. Cl.**[7] **C12N 15/00**

(52) **U.S. Cl.** **536/23.4**; 536/23.1; 536/23.5; 530/350; 530/387.3; 530/395; 435/69.7

(58) **Field of Search** 536/23.4; 530/350, 530/395; 514/2; 435/69.1, 69.7, 320.1, 325, 252.3, 254.11

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,657,853	*	4/1987	Freytag	435/7
5,304,640		4/1994	Lasky et al.	536/23.5
5,360,733	*	11/1994	Takada et al.	435/193
5,464,778	*	11/1995	Cummings	436/503

FOREIGN PATENT DOCUMENTS

480408	4/1992	(EP) .
WO 9001546	2/1990	(WO) .
WO 9100868	1/1991	(WO) .
WO 91/06632	5/1991	(WO) .
WO 92/01718	2/1992	(WO) .
9209698 *	6/1992	(WO) .
WO 92/16612	10/1992	(WO) .
WO 92/19735	11/1992	(WO) .
WO 9303052	2/1993	(WO) .
WO 9304199	3/1993	(WO) .
WO 9309250	5/1993	(WO) .
WO 9313220	7/1993	(WO) .
WO 9315228	8/1993	(WO) .
WO 94/07917	4/1994	(WO) .
WO 94/10309	5/1994	(WO) .
WO 94/11498	5/1994	(WO) .

OTHER PUBLICATIONS

Darnell et al., Molecular Cell Biology, pp. 54, 55, 258–260, 1986, Scientific American Books.*
Norgard, et al., J. Biol. Chem. 268:12674–12774 (1993).
Johnston et al., Cell 56:1033–1044 (1989).
Sako et al., Cell 75:1179–1186 (1993).
Moore et al., J. Cell Biol. 118(2):445–446 (1992).
Bierhuizen and Fukuda, Proc. Nat'l Acad. Sci USA 89:9326–9330 (1992).
Larsen et al., J. Biol. Chem. 267(16):11104–11110 (1992).
Maemura and Fukuda, J. Biol. Chem. 267(34):24379–24386 (1992).
Moore et al., J. Biol. Chem. 269(37):23318–23327 (1994).
Steininger et al., Biochem. & Biophys. Res. Comm. 188(2):760–766 (1992).
Zhou, et al., J. Cell Biol. V.115, 557–564, (1991) The Selectin GMP–140 Binds to Sialylated, Fucosylated Lactosaminoglycans on Both Myeloid and Nonmyeloid Cells.
Aruffo, et al., Cell, vol. 67, 35–44, (1991) CD62/P–Selectin Recognition of Myeloid and Tumor Cell Sulfatides.
Polley, et al., Proc.Natl.Acad.Sci. USA vol. 88, 6224–6228 (1991) CD62 and endothelial cell–leukocyte adhesion molecule 1 (ELAM–1) recognize the same carbohydrates ligand, sialyl–Lewis^x.
Picker, et al., Cell, vol. 66, 921–933 (1991) The Neutrophil Selectin LECAM–1 Presents Carbohydrate Ligands to the Vascular Selectins ELAM–1 and GMP–140.
Larkin, et al., J.Biol.Chem., vol. 267, 13661–13668 (1992) Spectrum of Sialylated and Nonsialylated Fuco–oligosaccharides Bound by the Endothelial–Leukocyte Adhesion Molecule E–selectin.

* cited by examiner

Primary Examiner—Yvonne Eyler
Assistant Examiner—Eliane Lazar-Wesley
(74) *Attorney, Agent, or Firm*—Lahive & Cockfield, LLP; Amy E. Mandragouras, Esq.

(57) **ABSTRACT**

Fusions proteins comprising P-selectin ligand proteins are disclosed, including fusions with immunoglobulins, BMPs, AGP and IL-11. Polynucleotides encoding such fusions are also disclosed.

16 Claims, 30 Drawing Sheets

US005510102A

United States Patent [19]

Cochrum

[11] Patent Number: 5,510,102

[45] Date of Patent: Apr. 23, 1996

[54] **PLASMA AND POLYMER CONTAINING SURGICAL HEMOSTATIC ADHESIVES**

[75] Inventor: **Kent C. Cochrum**, Davis, Calif.

[73] Assignee: **The Regents of the University of California**, Oakland, Calif.

[21] Appl. No.: **377,775**

[22] Filed: **Jan. 23, 1995**

[51] **Int. Cl.**[6] **A61K 38/36**; A61L 25/00

[52] **U.S. Cl.** **424/78.08**; 424/530; 602/52; 128/DIG. 22

[58] **Field of Search** 514/772.2; 424/78.08, 424/530

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,373,519	2/1983	Errede et al.	128/156
4,599,209	7/1986	Dautzenberg et al.	264/7
4,664,105	5/1987	Dautzenberg et al.	128/156
5,226,877	7/1993	Epstein	604/35
5,292,362	3/1994	Bass et al.	106/124

Primary Examiner—Peter F. Kulkosky

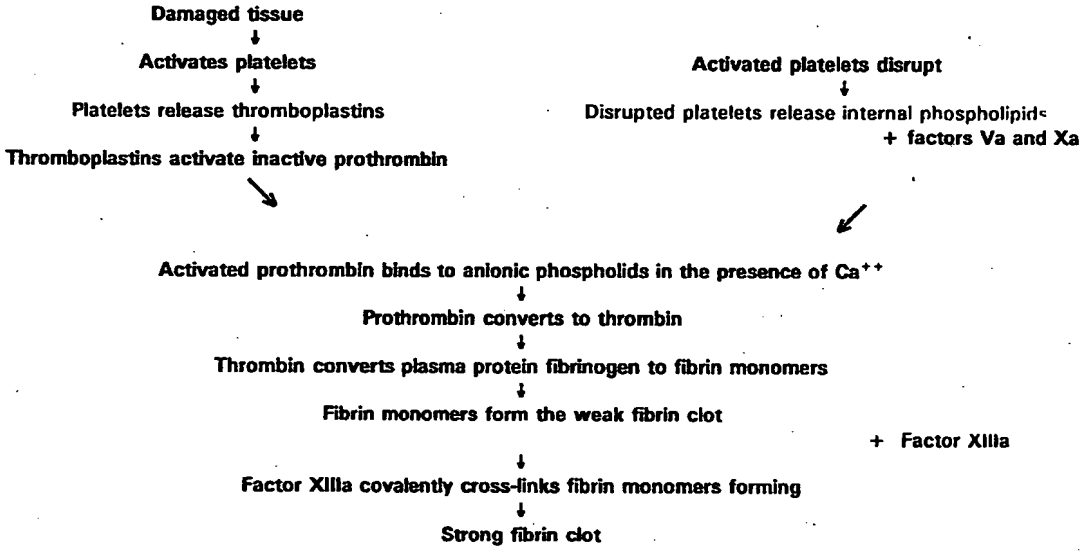
Attorney, Agent, or Firm—Hana Verny

[57] **ABSTRACT**

Autologous platelet-rich plasma and a biocompatible polymer containing hemostatic adhesive agents. The agents have strong hemostatic properties when applied to a bleeding wound or vessel.

17 Claims, 2 Drawing Sheets

PHYSIOLOGICAL PROCESS OF COAGULATION



US005378464A

United States Patent [19]

McEver

[11] Patent Number: 5,378,464

[45] Date of Patent: Jan. 3, 1995

[54] **MODULATION OF INFLAMMATORY RESPONSES BY ADMINISTRATION OF GMP-140 OR ANTIBODY TO GMP-140**

[75] Inventor: **Rodger P. McEver, Oklahoma City, Okla.**

[73] Assignee: **Board of Regents of the University of Oklahoma, Norman, Okla.**

[21] Appl. No.: **320,408**

[22] Filed: **Mar. 8, 1989**

[51] **Int. Cl.**[6] **A61K 39/395; A61K 37/02**

[52] **U.S. Cl.** **424/143.1; 514/8**

[58] **Field of Search** 514/8, 23; 530/350, 530/381, 395, 387, 387.1, 387.5, 388.22; 424/85.8

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,605,644 8/1986 Foker 514/45
5,114,842 5/1992 Plow et al. 530/388.22

FOREIGN PATENT DOCUMENTS

0101185 2/1984 European Pat. Off. A61K 9/08

OTHER PUBLICATIONS

Issekutz, A., et al., *Laboratory Invest.* vol. 49, No. 6, pp. 716–724 (1983).
McEver, R., et al., *J. Biol. Chem.*, vol. 259, No. 15, pp. 9799–9804 (Aug. 10, 1984).
Stenberg, P., et al., *J. Cell. Biol.*, vol. 101, pp. 880–886 (Sep. 1985).
McEver, et al., *Blood* 70(5) Suppl. 1:355a, Abstract No. 1274 (1987).
Johnston, et al., *Blood* 70(5) Suppl. 1:352a Abstract No. 1264 (1987).
Muller-Eberhard, H., *Ann. Rev. Biochem.* 57:321–347 (1988).
Bevilacqua, M. P., et al., *Science*, vol. 243, pp. 1160–1165 (Mar. 3, 1989).
Siegelman, M. H., et al., *Science*, vol. 243, pp. 1165–1172 (Mar. 3, 1989).
Larsen, E., et al., *Cell*, vol. 59, 305–312 (Oct. 20, 1989).
Hamburger, S., et al., *Blood*, vol. 75, No. 3, pp. 550–554 (Feb. 1, 1990).
Johnston, G. I., et al., Cell, vol. 56, 1033–1044 (Mar. 24, 1989).
Brandley, B. K., et al., *Cell*, vol. 63, 861–863 (Nov. 30, 1990).
Springer, T. A., et al., *Nature*, vol. 349, pp. 196–197, (Jan. 17, 1991).
Goelz, S. E., et al., *Cell*, vol. 63, pp. 1349–1356 (Dec. 21, 1990).
Corral, L., et al., *Biochem. & Biophy. Res. Comm.*, vol. 172, No. 3, pp. 1349–1356 (Nov. 15, 1990).
Tiemeyer, M., et al., *Proc. Natl. Acad. Sci.*, vol. 88, pp. 1138–1142 (Feb. 1991).
Lowe, J. B. et al., *Cell*, vol. 63, pp. 475–484 (Nov. 2, 1990).
Walz, G., et al., *Science*, vol. 250, pp. 1132–1135 (Nov. 23, 1990).
Phillips, M. L., et al., *Science* vol. 250, pp. 1130–1131 (Nov. 23, 1990).
Bowen, B. R., et al., *J. of Cell Biol.*, vol. 109, pp. 421–427 (Jul. 1989).

(List continued on next page.)

Primary Examiner—Stephen G. Walsh
Attorney, Agent, or Firm—Kilpatrick & Cody

[57] **ABSTRACT**

A method using compounds inhibiting binding reactions involving GMP-140 to modulate an inflammatory response. The method is based on the discovery that GMP-140, released from the storage granules of platelets, endothelial cells, and megakaryocytes, and redistributed to the surface of the cells within seconds of activation by mediators such as thrombin, ionophores or histamine, binds to a ligand on neutrophils, and the plasma proteins C3*b* and protein S. Adhesion of the cells following activation is blocked directly by administration of antibody to GMP-140 or its ligand, or by competitive inhibition by administration of soluble GMP-140, the GMP-140 ligand, or the specific carbohydrate portion of the ligand bound by GMP-140.

9 Claims, 6 Drawing Sheets